DUE: 16/3/04

RMB

PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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RECEIVED
22 JAN 2004
CARPMAELS & RANSFORD
ACTIONED

PCT

WRITTEN OPINION
(PCT Rule 66)

CORRECTED VERSION

Date of mailing *(day/month/year)*	16.01.2004
REPLY DUE	**within 2 month(s)** from the above date of mailing
Applicant's or agent's file reference: P029441WO	
International application No.: PCT/GB 03/00211	International filing date *(day/month/year)*: 21.01.2003 — Priority date *(day/month/year)*: 22.01.2002
International Patent Classification (IPC) or both national classification and IPC: C12N9/12	
Applicant: EUROPEAN MOLECULAR BIOLOGY LABORATORY et al.	

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22.05.2004

Name and mailing address of the international preliminary examining authority:

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Authorized Officer
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I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-46 as originally filed

Claims, No.:

1-54 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

8, filed with the letter of 22-04-2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 28-30 (all entirely); 31,33-38 (all partially),

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28-30 (all entirely); 31,33-38 (all partially).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-26,31-42,44,48,52 (NO)
Inventive step (IS)	Claims	1-27,31-54 (NO)
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

Re Item III

According to Rule 66.1(e) PCT, claims relating to inventions in respect of which no international search report (ISR) has been established need not be the subject of international preliminary examination. As the subject-matter of claims 28-30 (all entirely) and 31, and 33-38 (all partially) has not been searched (see BOX I of the International Search Report), no preliminary examination has been carried out for these claims.

Re Item IV

The application lacks unity contradicting Rule 13 PCT. Rule 13 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept. The only common concept linking the two recognized inventions in the present application (see lack of unity section in the ISR) is the fact that a protease cleavage site is located near the boundary of the "cap" region and the SH3 domain. This concept is not considered as an inventive concept since it is neither novel nor inventive. A site recognized by a protease is very likely to be present in N-terminal locations of existing c-Abl proteins.

Many proteases are known, and under certain conditions they might cleave specifically or unspecifically at different locations of a protein. Thus, it is considered that any c-Abl or c-Abl mutant which might be cleaved at his N-terminus under certain conditions, would fall under the scope of claim 42, even the wild type c-Abl. Thus, such c-Abl proteins would not be necessarily related to invention 1. Since no other feature could be identified neither in the description nor in the claims that could be considered a "special" technical feature in the sense of Rule 13.2 PCT, each invention must be regarded as a separate potential invention. However, the IPEA has elected to carry out examination on the subject-matter of all claims.

Re Item V

1. The document numbering corresponds to the order of citation in the search report.

2. This communication is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D1 cited in the international search report would become relevant.

3. Claims 41 and 52 refer to a transgenic animal, which includes transgenic humans. The Applicant is suggested to exclude transgenic humans.

4. The IPEA considers that the identification of the "cap region" of Abl as an inhibitor of the Abl tyrosine kinase activity, involves an inventive step. Although, in the prior art there were suggestions that an intramolecular interaction in c-Abl could be responsible for such inhibition (see e.g. page 1514, left column, third paragraph of **D7**; or page 282, left column of **D6**), there is no indication in the prior art to the fact that the cap region would be responsible for a tyrosine kinase inhibition. Furthermore, although the skilled person could have discovered the effect of the "cap region" by using standard methods in the art, there is no indication that he would have done so.

5. However, the present set of claims does not meet the requirements of the PCT for the following reasons:

Lack of novelty

5.1 Claims 1-26, and 31-41 not only refer to the cap region but to a **"functional equivalent"** thereof. As no precise definition is given for such an expression, any compound which inhibits the Abl tyrosine kinase has been considered as a functional equivalent and thus, **the subject-matter of claims 1-26, and 31-41 is considered as not novel**, contravening the requirements of Article 33(2) PCT.

As examples **D3**, **D4** or **D5** disclose Abl protein kinase inhibitors, which are considered as functional equivalents of the cap region of c-Abl as far as there is no precise definition for such an expression. These documents also disclose the use of such tyrosine kinase modulators in therapy (see e.g. D3, corresponding to a patent application from the same Applicant as the present application).

5.2 **The subject-matter of claims 42, 44, 48, and 52 is also not novel.** A given protease under certain conditions might cleave at different locations of a protein, and thus, any c-Abl or c-Abl mutant which might be cleaved at his N-terminus under certain conditions, would fall under the scope of these claims, **even the wild type c-Abl** (for transgenic animals see e.g. page 181 of D2, left column, first two paragraphs).

Insufficient disclosure, lack of inventive step

5.3 **Claims 1-27, and 31-54** do not meet the requirements of Articles 6 PCT and Article 33(3) PCT, since the subject-matter of these claims **is not sufficiently disclosed and it does not involve an inventive step.**

The present application discloses the inhibition of c-Abl in vitro by using the N-terminal region of c-Abl (cap region). There is no sufficient evidence for the fact that such region would act as a tyrosine kinase inhibitor protein for any other tyrosine kinase, (and thus the subject-matter of the claims is not sufficiently disclosed). Accordingly, if the subject-matter of claim does not solve the technical problem in its whole scope, but only for a particular case (c-Abl tyrosine kinase activity), the claim as a whole can not be considered to involve an inventive step.

Lack of clarity

5.4 Furthermore, **claims 1-27 and 31-54, which make reference to the cap region of c-Abl, are not clear**, contravening the requirements of Article 6 PCT.

According to the PCT Preliminary Examination Guidelines, the meaning of the terms of a claim should, as far as possible, be clear for the person skilled in the art **from the wording of the claim alone**. "Each claim should be studied by the examiner giving the words the meaning and scope which they normally have in the relevant art, unless in particular cases the description gives the words a special meaning, by explicit definition or otherwise. Moreover, if such a special meaning applies, the examiner should, as far as possible, **require the claim to be amended whereby the meaning is clear from the wording of the claim alone**" (see Guidelines, Chapter III, Section 4.2).

No prior art document (excluding D1, cited as a P,X document) made reference to the "cap region of c-Abl", and thus the skilled person has not enough guidance as to the meaning of such expression. In contrast, a particular sequence or particular positions of a known protein would be clear features.

Industrial applicability

5.5 For the assessment of the present claims 36-38 and 40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO does not recognize as industrially applicable methods of treatment of the human body by surgery or therapy and diagnostic methods practised on the human or animal body. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.